Consensus Process to Develop Research Principles and Priorities to End TB in Children and Adolescents

Annual CAWG Meeting

November 11, 2024

OVERARCHING AIMS

- Achieve international consensus on the most important research principles and priorities that apply to TB research in children and adolescents

- Encourage research that adhere to the principles articulated and motivate the investment of resources into research that address key priorities.

Target audience: funding agencies, Ministries of Health, researchers

PRINCIPLES

- Principles that ensure inclusion of children and adolescents in TB research, when most relevant
- Facts that motivate the need to strengthen this research, focusing on high-priority areas

PRIORITIES

- Research that address key knowledge gaps and areas of clinical need

DELPHI PROCESS

- Aim is to collect expert-based judgments and to use them to identify consensus
- Classically, have the following characteristics:
  - Participation of experts
  - Standardized questionnaire is adapted for every new round of questions
  - Univariate analyses
  - Feedback of the results to the experts with the opportunity for them to revise their judgments
  - One or multiple repetitions of the questionnaire
- Number of rounds, selection of experts, definition of consensus vary

1. Writing team drafts initial principles and priorities
2. 1st voting round to approve or reject principles and priorities
3. Solicit feedback on rejected (or nearly rejected) items at annual CAWG meeting
4. Writing team edits or discards rejected principles and priorities, considers suggestions for additional principles and priorities
5. Next voting round to approve or reject principles and priorities
6. Repeat Steps 4 and 5 until no further edits are suggested
7. Report process and findings in a manuscript to be submitted for publication

PARTICIPANTS

Child & Adolescent TB Working Group

CHAIR: Moorine Sekadde (Uganda)

VICE CHAIR: Chishala Chabala (Zambia)

OTHER MEMBERS OF WRITING TEAM

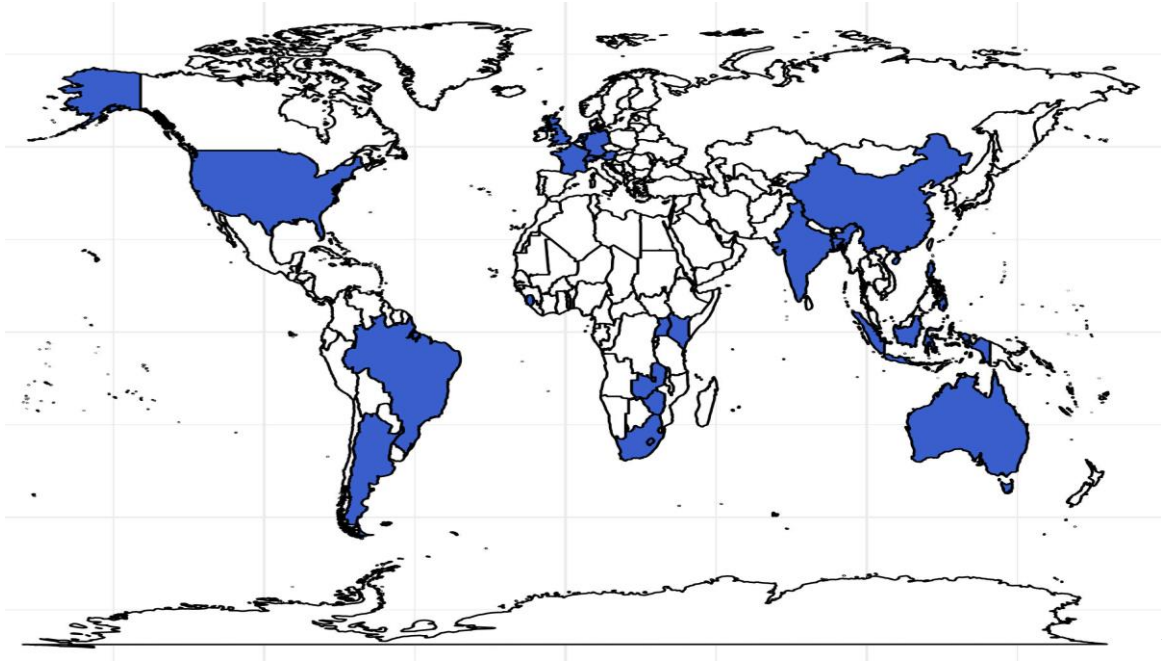
- Ben Marais (Australia)
- Steve Graham (Australia)
- Martina Casenghi (Switzerland)
- Lindsay McKenna (USA)
- Silvia Chiang (USA)
- James Seddon (UK, South Africa)
- Sabine Verkuijl (WHO)
- Annemieke Brands (WHO)
- Kerri Viney (WHO)
- Tiziana Masini (WHO)

INTERNATIONAL EXPERT PANEL

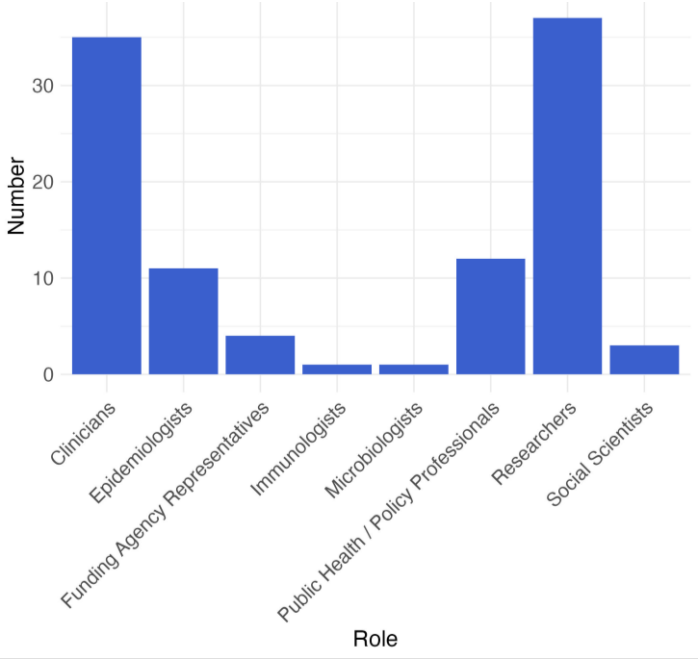
60 purposively sampled members of the CAWG, selected to achieve diversity in geographic areas and topics of expertise

COUNTRIES WHERE EXPERTS ARE BASED

Most based in low TB incidence countries but also working in high incidence settings



EXPERT ROLES



SCORING AND CONSENSUS

PRINCIPLES

- Scored from 1 (strongly disagree) to 5 (strongly agree)
- ≥85% of scores are 4 or 5

PRIORITIES

- Scored from 1 to 5 in 5 domains
- 5 scores averaged for overall score
- ≥80% of overall scores are ≥3.5

SCORE COMPONENTS (PRIORITIES)

Novelty	The answer to this research question is not currently known or able to be extrapolated from currently available evidence
Answerability	It is feasible to collect the data needed to answer this research question, and it is possible to do so in an ethical way.
Potential for translation	The answer to this research question will lead to an intervention.
Potential impact on disease burden or outcome	The answer to this research question will lead to the reduction of tuberculosis burden, morbidity, or mortality among children and adolescents.
Equity	The findings from this research question will reduce disparities in tuberculosis burden or outcome across settings and groups of children and adolescents.

DISCUSSION

Previous principle and discussion

Despite being preventable and treatable, TB kills an estimated 300,000 children and adolescents each year around the world (Dodd et al. Lancet Glob Health 2017;5:e898-e906; Chiang et al. J Adol Health 2023;72:323-331). Only with greater investment in research and development will this high mortality be prevented. **FAIL**

- Feedback: There are other contributors to mortality beyond R&D especially capacity to diagnose TB. The principle suggests that greater investment in R&D is the only contributor. Specify areas to target for example case finding, service delivery, treatment

- ? To what extent does R&D contribute to prevention of TB related mortality

Suggested changes

- Despite being preventable and treatable, TB kills an estimated 300,000 children and adolescents each year around the world **and most of these deaths are in children and adolescents who did not access diagnosis, treatment or prevention services** (Dodd et al. Lancet Glob Health 2017;5:e898-e906; Chiang et al. J Adol Health 2023;72:323-331).

- Greater investment in research and development **of tools to improve detection, treatment and prevention and in implementation research to increase access and coverage** is required to reduce this high mortality be prevented.

Previous principle and discussion

TB in children is a proxy for recent transmission. Therefore, the inclusion in epidemiological studies will enhance understanding of and inform interventions to reduce M. TB transmission. **BARELY PASS**

- Feedback: Depends on the study; concerns around epidemiologic linkage in clinically diagnosed individuals; anticipated high costs and complexities with including children in prevalence surveys; children infected with TB are potential transmitters later in life
- Is the problematic aspect of this principle the difficulty of conducting epidemiological studies in children (i.e., small % of microbiologically confirmed disease); vagueness of the term “epidemiological studies”; or other?

Suggested changes

- The **prevalence of TB infection and incidence of disease** in **young** children are proxies for recent transmission….
- …and therefore should be considered for **inclusion in epidemiological studies** and as **outcome measures for impact** in intervention studies that aim to reduce M. TB transmission.

Previous principle and discussion

With respect to the clinical presentation of TB, ability to produce sputum, sensitivity of microbiological assays, pharmacokinetics, and pharmacodynamics, adolescents. Therefore, adolescents should be included in adult diagnostic, treatment, and prevention studies, and studies should ensure they are recruited in sufficient numbers to generate confidence that study findings apply to adolescents. **FAIL**

- Feedback: There is need to have adolescents as a distinct population whether included in peds or adult studies. The young adolescents are not necessarily similar to adults with respect to the listed parameters.

- ? Is there need to specify age categories?
- Is the problematic part of this principle that younger adolescents resemble children more, and moreover, the age at which they begin to resemble adults varies?
- Or, is the problematic part of this principle that by suggesting adolescents be included in adult studies, they risk being neglected further, because they will be “lumped in” with adults?

Suggested changes

- With respect to the clinical presentation of TB, diagnostic approach and treatment pharmacokinetics and pharmacodynamics, adolescents (10-19 years) resemble adults. **On the other hand, there are aspects of care delivery and treatment support for adolescents that overlap with TB in children.**

- Therefore, adolescents should be considered for **inclusion in studies of both adults and children**, with findings reported by age to at least allow disaggregation of **young adolescents (10-14 years) and older adolescents (15-19 years)**.

RESEARCH PRIORITIES

Research Priority nr 1

CURRENT WORDING: Identify community settings outside of the household in which children and adolescents are at high risk for becoming infected with M. tuberculosis.

FAIL

❑ **Main feedback received:**

➢ NOVELTY has been questioned: data already exists but detailed analysis missing

➢ ANSWERABILITY:
- Determine origin of exposure may require molecular epidemiology to trace strains transmission
- Complexity, also due to low yield of bacteriological confirmation in children

➢ Uncertainty about IMPACT: translation would imply doing what we know we should already be doing

➢ Differentiate age groups: for older children and adolescents maybe more relevant

Research Priority nr 3

CURRENT WORDING: Identify effective ways to reduce M. tuberculosis transmission in educational settings while limiting the amount of time that students with transmissible tuberculosis are excluded from attending classes.

FAIL

- **Main feedback received:**
  - Could be combined with previous question
  - Impact on TB morbidity and mortality is not clear/evident but can have impact on loss of education, stigma, mental health
  - Two priorities included here and would not try to balance those 2 aspects in one priority. Main/broader issue underlying transmission in schools would me more focused around case finding/early diagnosis, access to TPT, infection control principles.

FEEDBACK NEEDED

1. Drop Q1
2. Rephrase Q1 and Q3 but keep them separate
3. REWORD to merge Q1 and Q3 (but need to avoid to include too many concepts in one single statement/priority)

SUGGESTED REWORDING for merged Q1 and Q3 could be:

-Define risk of transmission in educational settings and identify effective approaches and TB service delivery models to minimize it

-Identify approaches to minimize impact of TB care on isolation requirements, school loss/interruption

Research Priority nr 11

CURRENT WORDING: Determine the optimal screening frequency at which children and adolescents in high-risk groups should be screened for tuberculosis infection and disease.

BARELY PASSED

❑ **Main feedback received:**

➢ Too general
-Need to specify high risk groups
-need to define screening approaches (symptom-based screening, CXR-based screening ?)

➢ Prioritize screening for TB disease vs screening for TB infection

➢ Maybe better answered by modelling

FEEDBACK NEEDED

1. Screening for TB disease only for both TB disease and TB infection?

2. Focus on high risk groups only? If YES, which ones- for CALHIV frequnecy of TB screening already defined (e.g malnourished, with penumonia, sick children attending facilities etc)

3. Is it a priority to assess frequency also for symptom-based approach (simple, low/no costs, limited investments required for implementation)?

Rewording to be informed by feedback received on the questions above